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09/424,482	02/29/2000	YEN CHOO	PM264974	8038

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	33

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/424,482	CHOO ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8 and 10-28* is/are pending in the application.

4a) Of the above claim(s) *4,5,8 and 10-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 6-7, 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Response to Arguments

Applicants maintain their traversal of the restriction requirement. Applicants argue that Annex B at MPEP at p. AI-53 provides in relevant part, guidelines for applying unity of invention. Claim 4 is argued to incorporate all the elements from claim 1 and thus constitutes a dependent claim in the same category as claim. 1. It is further argued that according to the cited guidelines, it is irrelevant whether or not claim 4 contains a further invention than claim 1. In response, applicants have taken out of context the relevant part in the MPEP that states "If the independent claims avoid the prior art and satisfy the requirement of the unity of invention no problem of lack of unity of invention arises in respect of any claims that depend on the independent claims." The prior art below clearly shows that a claim to the independent claim does not render obvious the dependent claim 4. Applicants further argue that claims 19 and 23 constitute respectively processes for manufacture and use incorporating the product of claim 1. The criteria regarding different methods of manufacture, uses and patentable distinctness are criteria for conventional

restriction practice for applications filed under 35 USC 111(a). In response, the restriction practice for U.S. filed application does not necessarily follow the PCT lack of unity of invention. Be it as it may, as stated in the cited MPEP, (i), in addition to an independent claim for a given product, an independent claim for a process ***specially adapted*** for the manufacture of said product and an independent claims for use of said product. Thus, the claimed process is not specially adapted for the claimed product. The claimed product can be made by other processes such as by prokaryotic, bacteriophage, in vitro utilizing different cells, expression vectors and/or primers. The library of Group I can be used as therapeutic agents as stated at pages 29-30. Rather, than the method in Group IV of using the library to determine the presence of a target nucleic acid molecule. Accordingly, in view of the prior art, the different inventions of Groups I-IV are distinct and different, Taken as a whole, each of the Groups contains additional features constituting different patentable subject matter over the prior art. A prior art reference anticipating e.g., Group I would not render obvious the other Groups of the claimed inventions.

The requirement is still deemed proper and is FINAL.

Status of Claims

Claims 1-2, 4-8 and 10-28 are pending in the application.

Claims 4-5, 8, 10-25 are withdrawn from consideration.

Claims 3 and 9 have been cancelled in the Present Amendment, 3/25/03. Claims 26-28 have been added in the present amendment.

Claims 1-2, 6-7 and 26-28 are under examination.

Specification

The submission of a new abstract obviates the objection to said abstract.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-2, 6-7 and 26-28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility for reasons advanced in the last Office action.

Response to Arguments

Applicants admit that in the present case, it is known that the zinc finger proteins of the claimed library have the general property of sequence-specific binding to a target sequence. But argue that the specification expressly discloses

at least three utilities including diagnostics, research tools and therapeutic. In response, as admitted, these are general utilities, not specific utilities. There is no evidence of record, either in the instant specification or in the prior art teachings, that a library, as claimed has been used as diagnostic or therapeutic. As to the argued utility as a research tools, Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. Further, In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible compounds the utility of which has also not been identified. *Brenner*, 148 USPQ at 690.

It is argued that any of the cited general utilities is credible given the nature and mechanism of zinc finger proteins and the state of the art. Zinc finger proteins are proteins that bind specific DNA target sequences to modulate the expression of a gene. Other reagents that perform similar functions (e.g., DNA probes and antisense RNAS) are well known to be useful for such purposes. There is no reason to think that a zinc finger protein that binds a specific sequence would be less useful than a DNA probe that binds the same sequence or that a zinc finger that modulates a gene would be less useful than an antisense RNA that

modulates the same gene. In reply, the specification does not recite that the diagnostics, therapeutics utilities or which of these general utilities correlate to the binding effects of the library of proteins. It cannot be readily ascertained from the teachings in the disclosure, what exactly the disease that has been diagnosed or therapeutically treated by a collection (library) of different zinc finger polypeptides. Applicants' correlation of the instant library to the single probe or antisense is inappropriate. The effect of a single compound cannot be equated to a library (collection) of compounds. A library containing all inconceivable reaction of compounds can raise all inconceivable effects. There is yet a single assay that can determine the effect of each of the zillions of compound in the library. To date this is still an insurmountable task faced by skilled in the art for a created library of compounds.

Applicants argue that because the utilities are credible for reagents such as probes and antisense RNA having analogous functions to zinc finger proteins, they are credible for zinc finger proteins too. In reply, the use of library as a probe is not disclosed in the specification. Thus, applicants' arguments are not commensurate in scope with the claims. As stated by applicants, all compounds are known to bind one way or another

to a target. It is therefore questionable as to the specific or resultant utility of a binding compound.

Applicants admit that the Examples in the specification may focus on isolation of zinc finger proteins with a given binding specificity rather than illustrating uses of zinc finger proteins. But argue that the latter readily follows from the former. It is not difficult to see how the zinc finger protein can be used in a diagnostic assay for detecting that target sequence. In response, there is nothing in the specification as to the disease being diagnosed either by the single protein, let alone a library of protein. All of the examples provided in the disclosure describe a method of making the library. No intended use is exemplified or demonstrated in any of the given Examples.

Applicants called the examiner's attention to the uses of zinc finger proteins as disclosed by Choo. Each case has to be treated on its own merits. As stated, the Examples do not present a single utility for the single protein, let alone for the library of proteins.

Thus, the claimed library does not have a specific utility.

Claims 1-2, 6-7 and 26-28 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a practical asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed

invention as a therapeutic agent or as a pharmaceutical or even diagnosis. It is not apparent from the specification the type of diseases, if any, diagnosed by the claimed library.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 6-7 and 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The as-filed specification fails to provide a description for a first and second adjacent finger of an alpha helix. Applicants point out support for said term at page 7 and page 9. However, none of the cited sections reveal said language where the first and second random peptides are in the adjacent finger of an alpha helix. Rather, as disclosed at page 9, line 16-20, positions -1, 1, 2,3, 5 and 6

are varied in a first zinc finger and positions -1, 1, 2, 3 in a second finger.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 6-7 and are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of the claims has been withdrawn in view of the amendments to the claims and cancellation of other claims.

However, the newly amended claims 1, 2, 6-7 and 26-28 are rejected under this statute as follows:

1. Claim 26 is indefinite in the recitation of a method. Claim 1 is drawn to a library not a method.

2. Claim 27 is unclear in the recited " ***at least***" positions -1, 1, 2, 3, 5, 6 of a first zinc finger and -1, 1, 2, and 3 of the second finger are randomized. If this is the least position that can be randomized, then it is not clear as to the other or maximum positions that can be randomized. This claim is

inconsistent with claim 1. The base claim 1 recites that at least one of the said positions is randomized.

3. Claim 1 is indefinite in the recitation of "at least partially randomized such that the randomization extends to cover at least one position." See the rejection in the last Office action. It is noted that applicants have not responded to this rejection. Therefore, it is believed that applicants are acquiescing therewith. Claim 1 is unclear as to the first and second adjacent finger in an alpha helix polypeptide i.e., what constitutes an adjacent finger in a helix.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 6-7 and 26-28 are rejected under 35 U.S.C. 103(a) as being obvious over anyone of Greisman et al (US Patent 6,410,248) or Rebar et al (U.S. 5,789,538) or Wu et al (PNAS).

Greisman discloses a zinc finger protein with a first, second and third fingers randomized at positions -1, 1, 2, 3, 5, and 6. FIG. 1A depicts the amino acid sequence and secondary structure of the Zif268 zinc fingers. Randomized positions correspond to residues -1, 1, 2, 3, 5, and 6 in each of the alpha helices and include every position that makes a base contact in one of the known zinc finger-DNA complexes. Greisman further discloses that based on a target site comprising, e.g., first, second, and third subsites, a polypeptide display library encoding variants of a zinc finger protein is constructed, where the variants have a first randomized finger and two constant fingers, both either on the N- or C-terminal side of the randomized finger. Fingers to be randomized and constant fingers are selected from known zinc finger proteins. The constant fingers bind to known subsites. The target site also comprises two known sites to which the constant fingers bind, as well as first, second, and third subsites. The known subsites are adjacent to the first, second, and third subsites. This target site is used to screen the library for a first zinc finger protein, where the first selected variant finger binds to the first subsite of the target site, and the constant fingers bind to the known sites. See e.g., the claims.

Rebar discloses at e.g., col. 3, lines 14-65 multifingered protein in which more than one finger has each been selected to bind to a specific subsite. In the multifingered protein, each finger binds to an adjacent and overlapping subsite. A zinc finger phage library is shown in Examples 1-3. Three pools of zinc fingers are used to construct a new phage vector in which each of three zinc fingers have been selected for binding to the adjacent and overlapping subsite. Rebar further discloses that the binding specificity and affinity of a zinc finger is largely determined to a large degree by the amino acid residues which contact the nucleic acids of the polynucleotide. There are four nucleic acid-contacting residues in zinc fingers that are primarily responsible for determining specificity and affinity. These four amino acid residues occur in the same position relative to the first consensus histidine and the second consensus cysteine. Specifically, these four amino acid residues define which three to four base pair [or subsites] the zinc finger prefers to bind. The first of the three critical amino acid residues is seven residues to the N-terminal side of the first consensus histidine and six residues to the C-terminal side of the second consensus cysteine. This is hereinafter referred to as the "-1 position". The other three amino acids are two, three and six residues removed from the C-terminus of

the residue at position -1, and are referred to as the "2 position", "3 position" and "6 position", respectively. The amino acid residues one and five residues removed from the C-terminus of the amino acid at the -1 position are also important to zinc finger specificity and binding strength. Positions one and five residues removed from the C-terminus of the amino acid at -1 are referred to as the "1 position" and "5 position", respectively. These amino acid residues at these six positions are referred to as the base-contacting amino acids. It is to be understood that in a given zinc finger protein, not all of the amino acids at these six positions contact the double stranded DNA.

Wu discloses a library of zinc finger proteins with random residues at defined positions, as claimed. See e.g., page 345, RESULTS up to page 347, Table 2.

Each of these references discloses the critical binding positions -1, 1, 2, 3, 5, and 6 of a zinc finger and the randomization of these sites in one finger. Each of these regions suggests randomization of the second finger based on the target subsites to which these fingers bind. It would have been obvious to one having ordinary skill in the art at the time the invention was made to chose which positions of the second finger

can be a random residue based on the subsites of the target, as taught by any one of the above cited references.

Newly amended claims 1-2, 6-7 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Choo et al (Current Opinion in Biotechnology).

Response to Arguments

Applicants admit that Choo et al discloses specific libraries of DNA encoding zinc finger polypeptides having at least one zinc finger having a random allocation of amino acids at certain specified positions. But argue that Choo does not identify which positions have a random allocation of amino acids if more than one finger is randomized in such a library. In reply, Choo positively discloses a partial randomized allocation of amino acids, the partially randomised zinc finger having a random allocation of amino acids at positions -1, 1, 2, 3 5 and 6 (page 432, col. 1). In addition it is argued that Choo (2) provides evidence teaching away from the presently claimed invention. It is urged that the article indicates that simultaneously randomizing each of three zinc fingers in a three-finger zinc finger protein is "unlikely to be practical in the near future" due to the large number of permutations (page 433, paragraph bridging cols. 1 and 2). In response, preceding

the alleged teaching away, Choo discloses that "importantly, because multiple fingers are selected *en* bloc, each will be optimized (subject to the limitations of library size- according to its position and context within the DNA-binding domain...more practicable approaches are at hand, availing ourselves of the modular nature of zinc fingers, we can assemble a DNA binding domain from appropriate combinations of individually selected fingers (Fig. 2b)....." Accordingly, Choo discloses a remedy for the argued disclosure of Choo as being teaching away from the claimed invention. It is further argued that the disclosure of randomizing zinc fingers individually and assembling selected zinc fingers in a modular fashion teaches away from simultaneously randomizing adjacent fingers, as claimed. Applicants' arguments are not commensurate in scope with the claims. The claims do not recite for a randomizing step. Rather, a library of polypeptides with random residues at the recited positions, i.e., a compound claim. Be it as it may, Choo discloses at page 433, col. 1 the obvious strategy to simultaneously randomized each finger in a multifinger library. Because of the alpha helical form of the polypeptide, a randomized residues adjacent with each others would have been obvious to one having ordinary skill in the art. Contrary to applicants' arguments, there is no requirement that a motivation

to make the modification be expressly articulated, In re Simon 174 USPQ 114 (CCPA 1972), if the limitations in the claims are expressly taught in the prior art.

Double Patenting

Claims 1-2, 6-7 and 26-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,007,988('988 patent)(Choo et al) for reasons set forth in the last Office action.

Response to Arguments

Applicants admit that Choo et al discloses specific libraries of DNA encoding zinc finger polypeptides having at least one zinc finger having a random allocation of amino acids at certain specified positions. But argue the claims do not identify which positions have a random allocation of amino acids if more than one finger is randomized in such a library. In reply, Choo positively discloses a partial randomized allocation of amino acids, the partially randomised zinc finger having a random allocation of amino acids at positions -1, +2, +3 and +6 and at least one of positions +1, +5 or +8, position +1 being the first amino acid in the alpha-helix of the zinc finger.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
June 13, 2003